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REVIEW

Food and Drug Administration Regulation of Medical Device Biotechnology, and Food and Food Additive Biotechnology

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ABSTRACT

The Food and Drug Administration (FDA) is facing a flurry of new products coming to market over the next few years that will be based on biotechnology. The agency will have to deal with state-of-the-art drugs and devices utilizing biotechnology as the developmental base. Also, many universities and companies are exploring the potential uses of biotechnology in developing new foods and food additives. This article will examine how the FDA is presently regulating medical device, and food and food additive biotechnology and the challenges confronting the agency in these areas in the future.

Index Entries: FDA regulations; medical device biotechnology, regulation of; food and food additive biotechnology, regulation of.

FOOD AND DRUG ADMINISTRATION REGULATION OF MEDICAL DEVICE BIOTECHNOLOGY

The FDA regulation of medical device biotechnology has been a constantly evolving process since 1980. The agency has attempted to respond to the biotechnology revolution through balancing the need for

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bioengineered devices in the marketplace against the congressional mandate that the agency assure the safety and efficacy of all medical devices marketed in this country. To understand the FDA's statutory authority and the evolution of its regulatory policy in this area, it is necessary to describe the statutory framework through which medical devices are regulated in the United States. A discussion follows concerning how biotechnology is regulated in medical device applications.

Classification of Medical Devices

When Congress passed the Medical Device Amendments (the Amendments) of 1976, the legislative intent was to apply different degrees of regulation to different degrees of risk (*1*). The drafters of the law centered the regulation around a three-tier classification scheme. Every device is to be placed in one of three regulatory classes. Class I devices are those noncritical products whose safety and effectiveness can be assured under the general provisions of the Amendments and under the general adulteration and misbranding provisions of the Federal Food, Drug, and Cosmetic Act (the Act) (*2*). The second category is class II and includes those devices for which specific performance standards can be established in order to assure safety and effectiveness (*3*). Class III is reserved for the most "risk-laden" devices that are required to undergo a review for safety and efficacy prior to marketing (*4*). This review is similar to the review for premarketing clearance for new drugs. These devices require premarket clearance because their safety and efficacy cannot be assured through either class I or class II controls or because they are intended for use in life-supporting or sustaining circumstances or present an unreasonable risk of illness or injury.

Devices on the market prior to the May 28, 1976 enactment date of the Amendments are treated differently from postenactment devices. For these "preenactment" or "old" devices, the FDA has set up a complex classification system, utilizing numerous panels of experts. An expert classification panel was created for each product category, with the mandate to categorize every device on the market into one of three classes. The FDA is then free to either accept or reject the panel's classification recommendation. If the FDA places the device into class III, then the mamufacturer must file a premarket approval application (PMA) or a product development protocol (PDP) or seek reclassification.

Postenactment devices are generally categorized as class III devices automatically unless they are substantially equivalent to a preenactment device or equivalent to any other class I or class II device (*5*). Under section 510(k) of the Amendments, manufacturers are required to provide the FDA with 90-days notice before a new or modified device may be marketed (*6*). The FDA will then review the material provided in the premarket notification (or, as it is commonly called, the "510(k) notice") to determine if the device is substantially equivalent to a preenactment device. If the FDA finds that it is not substantially equivalent to an old

device, the agency will advise the company that the device is a class III device and must therefore go through some premarket approval procedure, such as the filing of a PDP, PMA, or petition for reclassification. If the device is found to be substantially equivalent, the manufacturer will be able to get the product to market faster than if a PMA was required. The PMAs require much more data than a 510(k) notice and take much longer to be approved by the FDA.

Application of the Medical Device Statutory Scheme to Biotechnology

Bioengineered products used for clinical diagnostic purposes clearly come within the definition of a medical device, as set forth in the Federal Food Drug, and Cosmetic Act, 21 USC § 321(h)(1982). The bioengineered products that are encompassed by this definition are primarily diagnostic aids, such as reagents, antibiotic sensitivity disks, and test kits for in vitro diagnosis of disease. Specifically, the FDA has been analyzing DNA hybridization probes for genetic disease; DNA hybridization probes for infectious agents; antitumor antigen antibodies; antitransplantation antigen antibodies; antidifferentiation antigen antibodies; and antidrug antibodies. Veterinary medical devices are literally within the scope of the definition and the statute, but the FDA has not subjected veterinary devices to any premarket clearance requirements.

Over 100 bioengineered medical devices have been the subject of FDA review and regulatory action since 1981. The FDA has primarily regulated these devices under its premarket notification scheme. The agency first accepted a 510(k) notice for a bioengineered device on February 9, 1981, in connection with the Direct Fluorescent Antibody Test Kit.

The primary emphasis in biotechnology oversight at the FDA over the past ten years has been in the biologics and drug areas. Although there have been numerous products that have been considered by the agency in the device area, it has been the old Office of Biologics that first attempted to help industry in providing guidelines for hybridoma product development and approval.

Of some help to manufacturers in in vitro diagnostic hybridoma products have been the unpublished guidelines or regulatory memoranda generated by the Office of Biologics. On March 10, 1982, that office made public a memorandum entitled "Points To Consider In The Manufacture Of In Vitro Monoclonal Antibody Products Subject To Bureau Of Biologics Licensure." This document was later revised, and in a June 20, 1983 memorandum to manufacturers of monoclonal antibody products, the Chairman of the office of Biologics Hybridoma Committee gave further guidance.

It is not entirely unusual for the FDA to regulate by memorandum when the agency is hesitant to issue any formal guidance or open such guidance up to comment in the *Federal Register*. Thus, the Office of Biologics' information is, at present, the only informal written guidance in

the hybridoma product area and is significant to device manufacturers in that the same issues are relevant to both bioengineered devices and biologics. The Office of Biologics' authority, however, extends only to in vitro diagnostics employed in blood banking. That office's jurisdiction over in vitro devices has been limited to date to blood grouping sera, antihuman globulin, and antibody to hepatitis B surface antigen. All other in vitro bioengineered devices come within the purview of the Center for Devices and Radiological Health.

In its early guidance, the agency has specifically stated that there are four primary concerns for marketing bioengineered in vitro devices. Those concerns are sensitivity, specificity, stability, and the potency and consistency of the product. Absent formal guidance, the Points to Consider will in all likelihood be the basis for determining what issues will be crucial in agency premarketing review of the hybridoma product. The FDA has indicated recently that some further guidance will be forthcoming soon with respect to approval criteria for certain in vitro bioengineered products, especially over-the-counter test kits. Nevertheless, it appears that such guidance will again be in the guise of Points to Consider, and, thus, manufacturers will not have any opportunity to comment upon the FDA's conclusions.

PMA or 510(k) For Bioengineered Devices

One of the issues now facing the FDA is whether certain in vitro diagnostic devices should be approved under the PMA provisions of the Amendments or pursuant to the premarket notification provisions of section 510(k). The first approvals of in vitro hybridoma products, as noted, were indeed through the 510(k) acceptance process. These included hybridoma assays for immunoglobulin E, ferritin, human chorionic gonadotropin (HCG), and prostatic acid phosphatase.

The agency made an early decision that it should fully cooperate with industry in applying the 510(k) process in as many instances as possible. The FDA staff concluded that substantial equivalency should be evaluated in terms of the test results, not the assay systems or the technology involved. It was evident that the most important factor was whether the test results were essentially the same as obtained through other diagnostic methods when used to analyze clinical specimens. It has not mattered to the agency that the operative mechanisms of the two tests or the specific assay systems differed so long as the clinical information provided was the same.

The agency's position on substantial equivalency, as applied to bioengineered devices, makes sense when evaluated in terms of administrative efficiency. It is much easier to clear a product through a 510(k) notice in terms of FDA person-hours [20 for a 510(k) versus 2000 for a PMA] (*7*). Indeed, there may even be some support in the legislative history of section 510(k) that gives the agency some discretion in allowing a

product to proceed along the 510(k) premarket notification route if there is no question as to safety and effectiveness (*8*).

If a manufacturer can convince the FDA reviewers at an early meeting that there will be sufficient data to show that the device will be effective in its diagnostic use, then it is quite possible that the agency will allow the manufacturer to proceed along the 510(k) route. However, it is essential that the manufacturer not only convince the FDA that there will be sufficient effectiveness data, but also that there will be results similar to those from previous in vitro diagnostic tests.

The agency has created what many term the "hybrid 510(k)" to approve fairly novel hybridoma products, as well as novel products in other areas, such as surgical neodymium yttrium–aluminum–garnet (Nd:YAG) lasers. Rather than simply filing a premarket notification specifying the technological aspects of the in vitro tests, manufacturers have been required also to submit effectiveness data. The 510(k) thus looks a bit like a PMA, but can be cleared through the FDA review process much faster than a PMA. Unlike a PMA, FDA general counsel and advisory panel review is unnecessary for this "hybrid 510(k)."

One of the issues that the FDA will have to address in the near future is how it will handle in vitro hybridoma tests that provide different data than that provided by conventional tests. If there is no conventional analog to a new hybridoma test, the question is whether the agency will find a lack of substantial equivalency and require the filing of a PMA.

It is the view of many in the field that the agency will do everything in its power to allow a company to proceed with the 510(k) submission so long as the data generated from the novel in vitro tests are not critical to the health of the patient (*9*). For novel devices that are critical to the health of the patient, such as products designed to support or negate diagnosis of malignant diseases, the FDA may decide to require the submission of a PMA.

For noncritical products, however, the FDA might reason that the PMA route is not necessary to assure the safety and efficacy of the device. The hybrid 510(k) will still give the agency some efficacy data. Such a reading of the statute is somewhat supported by the legislative history (*10*), but is even more strongly dictated by the necessity of the administrative process. Requiring PMAs for all arguably novel in vitro bioengineered devices could cause administrative chaos in the evaluation process at the agency. These issues are being evaluated by the FDA at this time, and a better idea as to agency policy on the 510(k) process should be forthcoming over the next year.

Summary

The future for medical devices developed through biotechnology is bright. New tests for acquired immune deficiency syndrome, chlamydia, and other public health threats are being approved by the agency in re-

cord time. One can expect that many new bioengineered medical devices will be approved for marketing over the next few years. The agency has adapted well to the challenges of this new technology and there should be few obstacles to progress in the area under the creative approach the agency has adopted.

FDA REGULATION OF FOOD AND FOOD ADDITIVE BIOTECHNOLOGY

There has been a revolution in food biotechnology similar to that experienced in the medical device biotechnology area. In its broadest sense, biotechnology is the application of biological systems and organisms to technical and industrial processes. When viewed in that sense, use of biotechnology to produce and process food is not new. In fact, man first used biotechnology over 10,000 years ago when microorganisms were unknowingly used to help produce bread and alcohol.

Similarly, there is nothing unique about the idea of modifying the genetic composition of plants and animals that provide man with food. For thousands of years, farmers have been trying to improve plants and animals through various breeding techniques. In the twentieth century, these efforts have become more systematic and more successful with the recognition that traits are passed from one generation to another in an orderly fashion.

Notwithstanding the fact that neither the concept nor the use of biotechnology in the food industry is novel, the available biotechnological techniques have been revolutionized in the past decade (*11*). Recombinant DNA (recDNA) allows the manipulation of genetic material with far greater precision and far more speed than in the past. Somatic hybridization offers new possibilities for obtaining interspecies combinations of genetic traits that could not occur through natural breeding (*12*). New methods of culturing microorganisms, particularly when paired with recDNA techniques, can yield mass quantities of organic chemicals; many of these chemicals have important food applications.

Under the Federal Food, Drug, and Cosmetic Act (*13*), bioengineered food products are regulated by the FDA. Although there is no existing federal regulation directed solely at biotechnology, it is clear that the FDA intends to regulate bioengineered food and food additives under its present statutory scheme (*14*). A brief description of that scheme follows, with an explanation of how the scheme will be applied to food and food additive biotechnology.

Regulation of Foods and Food Additives

Under the Act, any product that is considered a "food" (*15*) can be marketed without undergoing premarket clearance. In fact, there is no

requirement that the FDA even be notified that a company intends to market a food. However, to qualify as a food that can be marketed without preclearance by the FDA, the substance must be "generally recognized as safe" (GRAS). As will be discussed in greater detail later, traditional foods are GRAS, but a bioengineered version of a traditional food may not be so considered. An example is a potato with a high level of toxicity. Through genetic modification, potatoes with a high alkaloid content have been created. A product that is not GRAS (such as, possibly, this new potato) would be considered a food additive and must be aporoved through a petition process at the FDA.

Food additives are regulated quite differently than food. Food additives, unlike food, have to undergo premarket review and cannot be marketed unless comprehensive safety testing has been performed and submitted to the FDA. A food additive is defined under the Act as:

> Any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (*16*).

A substance that is a food additive can be introduced into food or come into contact with food only if the FDA has issued a regulation allowing its use. Any food additive that is not the subject of an approved food additive regulation is deemed to be unsafe by the agency (*17*). In turn, any food that contains an unsafe food additive is deemed to be adulterated (*18*) and is vulnerable to enforcement action by the agency. To date, the FDA has received no food additive petitions for bioengineered foods, but expects such petitions shortly.

A substance is considered GRAS if it is

> . . . generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use (*19*).

A substance that is GRAS for its intended use is not considered a food additive and, therefore, is not subject to the food additive requirements discussed above. Without going into greater detail as to the intricacies of this statute, it is clear that a major issue that will be facing biotechnology companies is whether bioengineered food will be considered a freely marketable food, a GRAS substance, or a food additive that would require review through the FDA premarket review process.

Application of FDA Statutory Scheme to Food Biotechnology

The FDA has tangentially addressed the issue of the status of bioengineered foods in its regulations. The agency stated that it will review the following substances to determine if they are still GRAS:

> Any substance of natural biological origin that has been widely consumed for its nutrient properties in the United States prior to January 1, 1958, without known detrimental effect, for which no health hazard is known, that has had significant alteration of composition by breeding or selection after January 1, 1958, where the change may be reasonably expected to alter the nutritive value or the concentration of toxic constituents (*20*).

Thus, any GRAS substance that is modified by any biotechnological technique—including classical genetics and recDNA—may have the current validity of its GRAS status questioned by the FDA.

The critical issue will be whether the new variety of substance significantly differs from its GRAS precedessors in nutrient or toxic concentration (*21*). If deliberate genetic alteration causes a significant change in the substance's chemical makeup, the product may lose its GRAS status and become a food additive that will require submission of data to prove its safety to the FDA.

Another issue facing the FDA will be whether certain bioengineered foods are properly labeled. When should a tomato no longer be called a tomato? At what point has an organism been sufficiently altered so that it can no longer accurately be identified by the same name as the species from which it derived the bulk of its genes? The FDA in the future will have to develop guidelines identifying the point at which genetically modified products might need new or supplementary names to avoid misleading consumers. This point would probably be reached when bioengineering results in the alteration of a major attribute that helps characterize the product for consumers. If the FDA decides a food is misbranded because of a misleading name, it can take enforcement action (*22*).

The FDA's good manufacturing practice regulations also have an impact upon bioengineered food additives (*23*). If a food additive manufacturer is employing biotechnology to manufacture a traditional approved food additive, will the FDA require a food additive petition describing the new process in detail? Does the difference in manufacturing method change the regulatory status of the product? Because of the extra expense and delay, requiring a food additive petition because of a manufacturing process change would hamper, if not preclude, the commercialization of many bioengineered food additives. Under FDA's current food additive regulations, one could pervasively argue that a new food additive manufacturing method, including bioengineering, would not require a new food additive petition for an already approved food additive. With only a few exceptions, FDA's food additive regulations do not specify the method of manufacture. The regulations address only the end product, not the methods by which the end product is obtained. Instead, each regulation sets forth requirements for the final substance's purity and identity.

Notwithstanding this fact, the FDA has intimated that food additives made through the new biotechnology may be subject to the food additive petition requirement (*24*). This issue will be resolved in the not too distant future when the FDA receives numerous inquiries concerning how the agency will regulate food additive and food biotechnology.

CONCLUSION

New biotechnology will ultimately have a significant and broad-based impact on American agricultural and food processing industry. Neither the FDA nor other government agencies believe that advances in biotechnology require any adjustment in the regulatory scheme. Accordingly, edible substances produced through the new biotechnology will undergo essentially the same review process as their conventionally manufactured counterparts. Nevertheless, it is clear that many policy decisions will have to be made within the FDA and other agencies to assure the safety of the products under the present statutory scheme and to assure that overregulation does not hinder the availability of beneficial bioengineered products to the public.

REFERENCES

1. *See* Rogers, *Medical Device Law—Intent and Implementation*, **36** *Food Drug Cosm. L. J.* 4 (1981).
2. **21** USC § 360c(a)(1)(A)(1982)
3. *Id.* § 360c(a)(1)(B).
4. *Id.* § 360c(a)(1)(C).
5. *Id.* § 360c(f)(1).
6. *Id.*§ 360(k).
7. Industry has relied heavily on the 510(k) process. Over 25,000 510(k) submissions have been filed with the FDA since 1976. In 1985, the FDA expects to review 5200 510 (k) notifications, compared to 95 PMA applications. Kahan, *Premarket Approval or Premarket Notification: An Update* **6** *Medical Device & Diagnostic Industry*, **24** (1984). This popularity is understandable since 98% of all 510(k) notices are accepted by the FDA. Kahan, *Premarket Approval versus Premarket Notification, Different Routes to the Same Market*, **39** *Food Drug Cosm. L. J.*, 510, 517 (1984). For a full explanation of the medical device approval processs and appellate options when adverse approval decisions are received, *see* O'Reilly, *Food and Drug Administration*, § 18–17 (1984).
8. H. R. Rep. 893, 94th Cong, 2d Sess. **36** (1976).
9. Bozeman, *The Regulation of Hybridoma Products*, from the proceedings of the Health Industry Manufacturers Association conference, entitled, *Impact of Hybridoma Technology on the Medical Device and Diagnostic Product Industry*, at 75–76 (1982); *see also* Miller, *The Impact of New Technology on Regulation by the FDA: Recombinant DNA Technology*, **36** *Food Drug Cosm. L. J.*, 345 (1981).
10. H. R. Rep. No. 893, 94th Cong., 2d Sess. **36** (1976).
11. *See* Commercial Biotechnology, An International Analysis, **3** (Office of Technology Assessment, 1984).

12. *See* Shanks, *The Regulation of Biotechnology Products as Toxics, HealthSpan* **21** (Feb. 1985); Comments, *Regulation of Genetically Engineered Foods Under the Federal Food, Drug, and Cosmetic Act,* **33** *AM. U.L. Rev.* 899, 913 (1984).
13. **21** USC §§ 301 *et seq.* (1982).
14. *See* **49** Fed. Reg. 50,856 (1984).
15. For the circuitous definition of food, *see* **21** USC § 321(f)(1982).
16. **21** USC § 321(s)(1982).
17. *Id.* § 348(a).
18. *Id.* § 342(a)(2)(C).
19. *Id.* § 321(s).
20. **21** CFR § 170.30(f)(2)(1985).
21. At one time, the FDA had proposed that a "significant alteration" would be a 10% or greater increase in a toxicant or a 20% or greater reduction in a nutrient. Spiher, *The Growing of GRAS,* **10**(3) *Hort. Science* 3,4 (1975). These numerical criteria were not adopted, leaving uncertainty as to the extent to which nutrient and composition can change without forfeiting GRAS status.
22. **21** USC § 343(a)(1982) ("A food shall be deemed to be misbranded—(a) If its labeling is false or misleading in any particular"); *see also id.* § 331 (prohibited act to cause introduction or delivery into interstate commerce of a misbranded food).
23. **21** CFR Part 110 (1985).
24. **49** *Fed. Reg.* 50,856. 50,879 (1984) ("Substances used in animal feeds, other than drugs, that are produced by recombinant DNA technology, are considered to be food additives and require approval of a food additive petition (FAP). Other products of new biotechnology may also be considered to be food additives"). For a full explanation of the food additive approval process and appellate options available in the event of adverse FDA decisions, *see* O'Reilly, *Food and Drug Administration,* § 11.08 (1984).